*Synthesis of 1, 4, 7-Cyclononatrione**

By Sin'iti KAWAI, Sanae TANAKA, Kenji TERAI,
Masami TEZUKA and Tarozaemon NISHIWAKI

(Received May 26, 1959)

The hydrocarbon $C_{20}H_{20}$ (III) with the complete skeleton of a regular pentagonal dodecahedron has not yet been known. Since the hydrocarbon, which shall be tentatively called "dodecahedrane", will be a very stable, strainless compound, an attemp of its synthesis has been started with the present work.

For the synthesis of dodecahedrane it is necessary to obtain the hypothetical *d, l*-tricyclic compound, $I+I'$, which shall be temporarily called " tricyclone ". Although there are four asymmetric carbon atoms in the molecule of tricyclone, only one pair of optical isomers, I and I', are possible and synthesis will lead to a racemate. The tricyclone, having three pairs each of carbonyl and active methylene groups, must be a very reactive compound. Condensation will begin with the collision of two molecules of triyclone in the following combination:

(1) $I+I'$; (2) $I+I$ and (3) $I'+I'$.

Case 1 may be divided into three divisions, a, b and c.

(a) Addition starts with cyclobutane ring formation, for instance, with addition of 2' to 1 and of 2 to 1'.

(b) Addition starts with cyclohexane ring formation, for instance, with addition of 2 to 1' and of 6' to 3.

(c) Addition starsts with cyclopentane ring formation, for instance, with addtion of 2 to 3' and of 4' to 3.

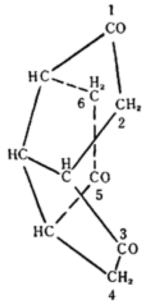
Both divisions a and b will lead to undefinable polymerization products, while division c may proceed to a dodecahedrane derivative under consecutive additions of 2' to 1, of 6 to 1', of 6' to 5 and of 4 to 5'.

In the presence of an appropriate agent (for instance sodium ethoxide, etc.), I and I' will be able to add to each other to give a hexahydroxydodecahedrane (II, R=OH) through the narrow reaction route, cace 1, division c, the yield being consequently expected to be small. As soon as the hexahydroxydodecahedrane is formed, it may probably suffer spontaneous dehydration, thus affording dodecahedrahexaene (IV). It is to be noted, that formula IV denotes only a limiting structure, because the conjugated hexaene ring V contained in formula IV will resonate with another limiting structure VA and that the double linkings in the molecule will not be restricted within the one hexaene ring, V↔VA, but will be distributed equally all over the whole system of the twenty carbon atoms. Consequently the dodecahedrahexaene is expected to be a rather stable compound, but its catalytic hydrogenation may afford the desired dodecahedrane (III).

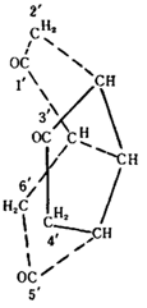
On the other hand, one possibility from case

---

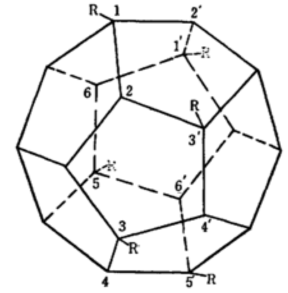
* Read before the Ninth Annual Meeting of the Chemical Society of Japan, Kyoto, April 5, 1956.



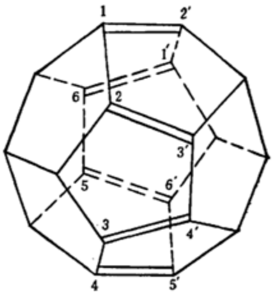
I



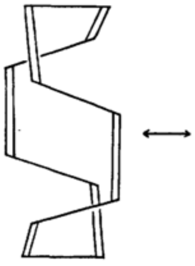
I′



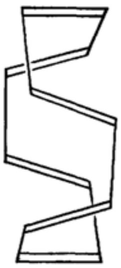
II R=OH ; $C_{20}H_{14}(OH)_6$
III R=H ; $C_{20}H_{20}$



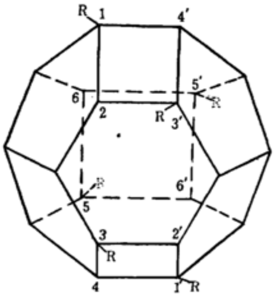
IV $C_{20}H_8$



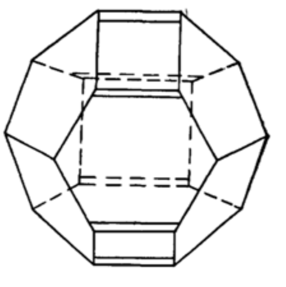
V



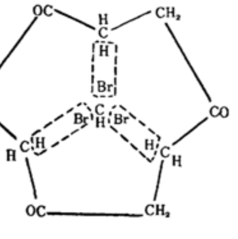
VA



VI R=OH ; $C_{20}H_{14}(OH)_6$



VII $C_{20}H_8$



VIII

2 will similarly lead to an optically active dimerization product VI (it shall be tentatively named "hexahydroxyisododecahedrane"). The corresponding product from case 3 will be the optical isomer of VI. In both compound VI and its optical isomer not only the cyclobutane rings but also the cyclohexane rings are strongly strained, because the latter may be forced to take an almost coplanar form. Dehydration at the instant of their formation may afford the same optically inactive isododecahedrahexaene $C_{20}H_8$, as shown by formula VII with arbitrary positions of the six double bonds.

Thus *d*, *l*-tricyclone, I+I′, may produce dodecahedrahexaene and isododecahedrahexaene along with a large amount of undefinable polymerization products from improper collisions among the tricyclone molecules.

Success depends on our ingenuity in the synthesis of *d*, *l*-tricyclone because we even expect that the tricyclone, if once formed, may condense spontaneously to give hexaene IV, although it may have to be separated from isohexaene VII. When condensed with bromoform, the compound given in the title of this paper, or 1, 4, 7-cyclononatrione (X), may give *d*, *l*-tricyclone accompanied by other condensation products (see VIII). This paper communicates the synthetical efforts paid by us for obtaining cyclononatrione (X). The syntheses of the so-called "medium ring"[1] compounds which are composed of 9, 10 or 11 methylenes are known to be difficult[2]. Some simple compounds among them, however, were synthesized recently by Prelog and Stoll's method[2], and it is especially noteworthy, that these medium ring compounds possess particular

---

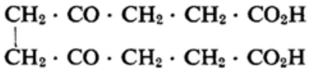
[1] H. C. Brown and M. Borkowsky, *J. Am. Chem. Soc.*, **74**, 1894 (1952).

[2] V. Prelog, *J. Chem. Soc.*, **1950**, 420.

internal strain (transannular effect)³⁾ when compared with other smaller or larger ring compounds. Apart from the question of transannular effect, there are fears lest cyclononatrione should suffer intramolecular condensation, and yet the first attempt adopted by us lay in the dry distillation of the barium salts of 4, 7-dioxodecanedioic acid (IX) according to Ruzicka's ring ketone syntheses⁴⁾. The acid IX was obtained early by Kehrer et al.,⁵⁾ later by Asahina and Fujita⁶⁾, and then by Hachihama et al.⁷⁾, through hydrolytic furan-ring fission of δ-furfurylidenelevulinic acid.

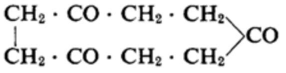
The acid IX was mixed with barium carbonate and pyrolysis was carried out by heating under reduced pressure. Indeed, a ketone was separated as its semicarbazone (m. p. 184° (decomp.)) from the neutral part of the distillate thus obtained, but the analytical value of its nitrogen content was too small to conclude that the trissemicarbazone of the triketone X was really obtained.

The yield of this undefinable semicarbazone in the above attempt was poor, but the synthesis turned out to be successful by boiling tetraethyl 2, 5 - diethylfuran - β, β, β′, β′ - tetracarboxylate (XIII) or triethyl 2, 5-diethylfuran-β, β, β′-tricarboxylate (XIV) with hydrobromic acid⁸⁾. The compounds XIII and XIV were synthesized by the following scheme.

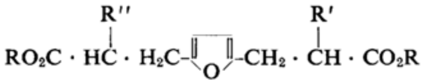


$$\begin{array}{l} CH_2\cdot CO\cdot CH_2\cdot CH_2\cdot CO_2H \\ | \\ CH_2\cdot CO\cdot CH_2\cdot CH_2\cdot CO_2H \end{array}$$

IX



X



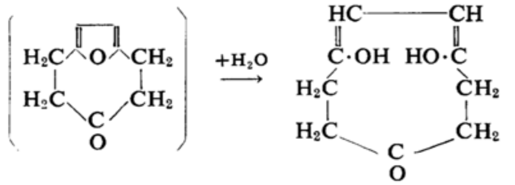
XI R = R′ = R″ = H

XII R = C_2H_5, R′ = R″ = H

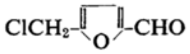
XIII R = C_2H_5, R′ = R″ = $CO_2C_2H_5$

XIV R = C_2H_5, R′ = $CO_2C_2H_5$, R″ = H

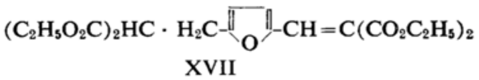
XV R = R″ = H, R′ = CO_2H



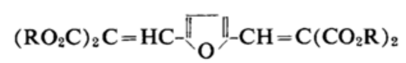
XX XXI



XVI



XVII



XVIII R = C_2H_5

XIX R = H

4, 7-Dioxodecanediocic acid (IX), when heated over its melting point, afforded 2, 5-diethylfuran-β, β′-dicarboxylic acid (XI)⁶ᵃ⁾,⁷ᵇ⁾, which was converted into its ethyl ester XII. Introduction of an ethoxycarbonyl group into the β-position of the latter was carried out according to Jone's procedure⁹⁾. From the reaction product, XIV was distilled at 132∼155°C/0.15∼0.27 mmHg in a poor yield. Without further purification the tarry residue was hydrolyzed with alcoholic potash to give 2, 5-diethylfuran-β, β, β′-tricarboxylic acid (XV) which, was identical with the hydrolysis product of XIV. 5-(Chloromethyl)-furfural (XVI)¹⁰⁾, on the other hand, gave tetraethyl 2-ethyl-5-vinylfuran-β, β, β′, β′-tetracarboxylate, (XVII) when treated with diethyl malonate. Catalytic reduction of XVII with platinum black afforded XIII. Neither did the latter distill out even in vacuo nor showed any sign of crystallization. It was immediately hydrolyzed with alcoholic potash, and then acidified with dilute sulfuric acid whereupon XV was obtained. These facts revealed that XIII was produced accompanied by XIV. Since it seemed noteworthy that, in the above-mentioned hydrolysis of XIII, only one ethoxycarbonyl group underwent decarboxylation simultaneously with hydrolysis, two more examples of the hydrolysis of related malonic ester derivatives were carried out. When XVII was shaken with aqueous potassium hydroxide at room temperature for a long time, and the reaction mixture was acidified, one ester group remained unchanged and one of the three hydrolyzed carboxyl groups underwent decarboxylation, thus a mono ester of a tricarboxylic

---

3) (a) V. Prelog and K. Schenker, *Helv. Chim. Acta*, **36**, 896, 1181 (1953); (b) A. C. Cope et al., *J. Am. Chem. Soc.*, **74**, 5885 (1952); (c) R. Robinson et al., *Chem. & Ind.*, **1953**, 944; (d) N. J. Leonard et al., *J. Am. Chem. Soc.*, **76**, 630, 3463, 5708 (1954).

4) L. Ruzicka et al., *Helv. Chim. Acta*, **9**, 249, 499 (1926); ibid., **11**, 496, 670 (1928).

5) (a) A. Ludwig and E. A. Kehrer, *Ber.*, **24**, 2776 (1891); (b) E. Hofacker and E. A. Kehrer, ibid., **28**, 917 (1895); c) E. Hofacker and E. A. Kehrer, *Ann.*, **294**, 165 (1896).

6) (a) Y. Asahina and M. Fujita, *J. Pharm. Soc. Japan*, **448**, 471 (1919); (b) Y. Asahina and M. Fujita, ibid., **470**, 331 (1931); (c) M. Fujita, ibid., **492**, 67 (1923).

7) (a) I. Hayashi, I. Kumashiro and Y. Hachihama, *J. Chem. Soc. Japan, Ind. Chem. Sec.*, (*Kogyo Kagaku Zasshi*), **57**, 299 (1954); (b) I. Hayashi and Y. Hachihama, ibid., **57**, 504 (1954).

8) L. Crombie, J. E. H. Hancok and R. P. Linstead, *J. Chem. Soc.*, **1953**, 3496.

9) V. H. Wallingford, A. H. Homeyer and D. M. Jones, *J. Am. Chem. Soc.*, **63**, 2056 (1941).

10) (a) Org. Syn., **14**, 62 (1934); (b) W. N. Haworth and W. H. H. Jones, *J. Chem. Soc.*, **1944**, 667.

acid (relative positions of its carboxyl and ester groups are ambiguous) was obtained. On the other hand, when tetraethyl 2, 5-divinylfuran-$\beta, \beta, \beta', \beta'$-tetracarboxylate (XVIII)[11,12] was hydrolyzed by heating with sodium hydroxide and acidifying with sulfuric acid, 2, 5-divinylfuran-$\beta, \beta, \beta', \beta'$-tetracarboxylic acid (XIX) was procured without suffering decarboxylation. Thus the malonic ester derivative (XVIII), in which the α-carbon atoms of the malonic ester groups are connected with α double linkings, undergoes only hydrolysis but not decarboxylation.

Now the tricarboxylic acid ester XIV was heated with 48% hydrobromic acid for 30 min. according to Linstead's method[8]. If ring closure occurred XX should be yielded. Although the compound XX is bicyclic with two double bonds at the bridged heads it may be capable of existence, because one of the two rings is eight-membered, hence belonging to an exceptional case of Bredt's rule[2]. As a matter of fact we could isolate the triketone X (or the keto form of XXI) as its trissemicarbazone (m. p. 176~177°C (decomp.)) from the neutral part of the reaction product, thus indicating the intermediate formation of the hypothetical bicyclic compound XX. In this case, only a little amount of XI was recovered from the acidic part, but the major amount became a black polymer which was rather soluble in water. The yield of the trissemicarbazone of X based on XIV ranged from 2 to 4%. Compounds, corresponding to mono- and bis-semicarbazones, were not detected. When the crude material of XIII was used as the starting material, X was obtained with poorer yields (0.5~1%). When XIV or XII were subjected to Dieckmann's ring closure with sodium and sodium methoxide, no ring formation was observed but XI besides the starting material were yielded.

The attempt to obtain the compound X from its semicarbazone was fruitless. When the trissemicarbazone was treated with alcoholic sulfuric acid, only a tarry matter was obtained as a neutral substance, which neither distilled in high vacuum nor gave any simicarbazone when treated with semicarbazide.

Experimental[13]

Dry distillation of 4, 7-dioxodecanedioic acid.—A small saber flask, which was wrapped with a copper wire gauze, was attached to a well chilled trap. 4, 7-Dioxodecanedioic acid (5 g., 1 mol.) and barium carbonate (4.3 g., 1 mol.) were powdered and intimately mixed and the whole was put into the flask. The flask was heated in vacuo gently at the beginning but later stronger with a free flame under constant moving. The oily distillate has an allyl-alcohol-like disagreeable smell. This pyrolysis was repeated five times and 25 g. in total of 4, 7-dioxodecanedioic acid gave 4.3 g. of the distillate. The distillate was dissolved in ether, washed successively with aqeous sodium bicarbonate, 10% sodium carbonate, and 5% sodium hydroxide, and finally with water, dried and evaporated. The yield of the neutral oily substance was 220 mg. Vacuum distillation gave a colorless oil, b. p. 205~248°C/0.1~0.14 mmHg; yield, 110 mg. Its semicarbazone was obtained in an usually way. Recrystallization from chloroform gave grayish white platelets, m. p. 184°C (partly decomp.).

Found: C, 42.68; H, 7.67; N, 34.70. Calcd. for $C_{12}H_{21}N_9O_3$: C, 42.47; H, 6.24; N, 37.15%.

Acidification of the aqueous sodium bicarbonate solution with sulfuric acid gave 50 mg. of an acidic material, m. p. 141~146°. The latter (28 mg.), without further purification, was titrated with 0.098 N sodium hydroxide, 2.8 cc. being consumed. When calculated for a dibasic acid its molecular weight is 230. This value roughly corresponds to that for 2, 5-diethylfuran-β, β'-dicarboxylic acid (XI) (m. p. 155°C with partial decomp., molecular weight 212). The sodium carbonate washing was acidified with dil. sulfuric acid and then shaken with ether. The ethereal solution, when evaporated, left an oily substance with strong phenolic smell. The sodium hydroxide washing behaved quite similarly. The phenolic oils of the two origins were therefore combined (250 mg. in total) and treated with *p*-nitrobenzoyl chloride. A small amount of crystals with m. p. 86~91°C was obtained but both its purity and quantity were insufficient for micro analysis.

Diethyl 2, 5-diethylfuran-β, β'-dicarboxylate (XII) and Diethyl 4, 7-dioxodecanedioate—A mixture of 2, 5-diethylfuran-β, β'-dicarboxylic acid (XI, 45 g.), absolute alcohol (300 cc.), benzene (150 cc.) and 2 drops of conc. sulfuric acid was subjected to azeotropic distillation. When the main bulk of alcohol distilled out further azeotropic distillation was repeated twice, with the addition of alcohol (100 cc.) and benzene (30 cc.) each time. Then the solvent was removed as much as possible. The residue was dissolved in ether, and the solution was washed successively with aqueous sodium bicarbonate and water, dried and evaporated. Vacuum distillation gave 36 g. (63%) of a colorless liquid, b. p. 155~161°C/4 mmHg. Redistillation gave XII in analytical purity as a liquid of b. p. 147~148°C/3 mmHg.

Found: C, 62.62; H, 7.58. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%.

During the above written manipulation of vacuum distillation the distillate over 180°C/4 mmHg. solidified in the condenser, and the residue in the distilling flask also solidified. Combined yield, 8 g. (13%). Recrystallization from petroleum ether (b. p. 40~55°C) gave diethyl 4, 7-dioxodecanedioate[5b] as colorless scales, m. p. 46~46.5°C. No melting point depression was observed, when mixed with an authentic specimen.

---

[11] W. F. Cooper and W. H. Nuttall, *J. Chem. Soc.*, **101**, 1074 (1912).

[12] W. F. Cooper and W. H. Nuttall, ibid., **105**, 2218 (1914).

[13] All melting points are uncorrected.

Found: C, 58.77; H, 7.75. Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75%.

Triethyl 2,5-diethylfuran-β, β, β′-tricarboxylate (XIV).—The above compound XII (13 g., 1 mol.) and diethyl carbonate (75 g., 6 mol.) were mixed well in a 500 cc. distilling flask, and to the mixture was slowly added a sodium ethoxide solution [2.3 g. metallic sodium in absolute alcohol (70 cc.)] with stirring. The solution gradually changed to pinkish yellow in color and yielded gray precipitates. Alcohol was removed slowly and carefully in a water bath. Dry benzene (30 cc.) was then added, and the solvent was removed by distillation as much as possible first on a steam bath, finally in an oil-bath (160∼170°C) in vacuo. After cooling water was added, the residue was acidified with sulfuric acid, and extracted with ether. The ethereal solution was washed with water, dried and evaporated. High vacuum distillation gave 3.3 g. (20%) of an oil which solidified on standing. B. p. 132∼135°C/0.15∼0.27 mmHg. Recrystallization from petroleum ether (b. p. 35∼45°C) with exterior cooling in dry ice gave XIV as colorless platelets, m. p. 28∼29°C.

Found: C, 60.29, H, 6.85. Calcd. for $C_{17}H_{24}O_7$: C, 56.99; H, 7.10%.

Tetraethyl 2,5-diethylfuran-β, β, β′, β′-tetracarboxylate (XIII).—5-(Chloromethyl)-furfural (XVI, b. p. 137∼138°C/5 mmHg, 16 g., 1 mol.) was added with cooling, to an alcoholic solution of magenesium salt of diethyl malonate [magnesium (2.5 g., 1 atom) dissolved in diethyl malonate (17 g., 1 mol.)]. The whole was kept standing at room temperature, and then refluxed for 1 hr. To this solution were added diethyl malonate (17 g., 1 mol.) and piperidine (0.5 cc.), and the whole was refluxed for 7.5 hr. The solvents were evaporated as thoroughly as possible, and then water was added to the risidue. After acidification with sulfuric acid, the reaction mixture was extracted with ether, washed with water and dried. Removal of the ether gave XVII as a dark red viscous oily substance which did not crystallize nor distil out on high vacuum distillation. The identification was carried out by way of its hydrolysis product (described later). An alcoholic solution (100 cc.) of the crude material of XVII (4.2 g., 0.1 mol.) was subjected to catalytic hydrogenation with platinum black (0.2 g.) as the catalyst, thereby 186 cc. (0°C, 760 mmHg; 0.085 mol.) of hydrogen gas being consumed during 60 min. Filtering off the catalyst and subsequent evaporation of alcohol gave a very viscous oily substance (XIII), its purification being fruitless.

2,5-Diethylfurane-β, β, β′-tricarboxylic acid (XV).—a) From XIV: A solution of XIV (3 g.) in 20% aqueous sodium hydroxide (50 cc.) was heated on a steam bath for 1 hr. The whole was acidified with sulfuric acid under cooling, salted out with table-salt, and extracted with ether. The ethereal layer was washed with water, dried and evaporated. The residue, after digestion with hot water (1 cc.), was allowed to stand for 2 or 3 days, thus yielding a little amount (0.3 g.) of crystals. Recrystallization from aqueous methanol afforded XV as colorless platelets, m. p. 102∼105°C (decomp.).

Found: C, 48.66; H, 5.32. Calcd. for $C_{11}H_{12}O_7 \cdot H_2O$: C, 48.18; H, 5.15%.

An aqueous solution of the above-obtained substance (0.265 g.) was titrated with 0.102 N aqueous sodium hydroxide, phenolphthalein being used as an indicator.

Found: 30.2 cc. Calcd.: 28.4 cc.

b) From XIII: Hydrolysis of the crude material XIII, already described above, gave the same XV.

Hydrolysis of Tetraethyl 2-ethyl-5-vinylfuran-β, β, β′, β′-tetracarboxylate (XVII).—The benzene (5 cc.) solution of the crude material of XVII (15 g.) was shaken with 20% aqueous potassium hydroxide (100 cc.) for 17 hr. at room temperature, then the whole was acidified with sulfuric acid under ice-cooling, and was extracted with ether. The ethereal layer was washed with water, dried and evaporated, thus a colorless solid matter (1 g.) was obtained. Recrystallization from wet benzene gave colorless plates, which melt at 148.5∼149°C with decomposition. Elementary analysis as well as titration revealed, that this compound ($C_{13}H_{14}O_7 \cdot \frac{1}{2}H_2O$) may be derived from XVII through hydrolysis. Simultaneous decarboxylation occurred in any one of the four ethoxycarbonyl groups contained in the molecule of XVII.

Found: C, 53.40; H, 5.67. Calcd. for $C_{13}H_{14}O_7 \cdot \frac{1}{2}H_2O$: C, 53.61; H, 5.91%.

The above-mentioned substance (0.301 g.) was titrated with 0.102 N aqueons sodium hydroxide, giving the following results.

Found: 22.1 cc. Calcd.: 19.6 cc.

2,5-Divinylfuran-β, β, β′, β′-tetracarboxylic Acid (XIX).—Tetraethyl 2,5-divinylfuran-β, β, β′, β′-tetracarboxylate (XVIII) (2 g.), which had been obtained by Cooper's method[12], was dissolved in 27% aqueous sodium hydroxide (50 cc.) and the whole was heated on a steam bath for 1 hr. The solution was then acidified with sulfuric acid, salted out with table-salt, and then extracted with ether. The ethereal layer was washed with water, dried and evaporated. The residue was dissolved in hot water (1 cc.) and then kept in a vacuum desiccator. Crystals which appeared during 10 days were collected, and recrystallized from ethyl acetate and then from hot water. Orange red plates, m. p. 218°C (decomp.); yield, 0.5 g. (39%).

Found: C, 46.01; H, 3.39. Calcd. for $C_{12}H_8O_9 \cdot H_2O$: C, 45.87; H, 3.21%.

The above-mentioned substance (0.317 g.) was titrated with 0.102 N aqueous sodium hydroxide, giving the following result.

Found: 40.5 cc. Calcd.: 39.0 cc.

Trissemicarbazone of 1,4,7-cyclononatrione (X).—The tricarboxylic acid triester XIV (5 g.) was mixed with 48% hydrobromic acid (30 cc.) and the whole was refluxed gently for 30 min. After cooling, the dark solution which occasionally contained a black solid matter was treated with water (100 cc.) and ethyl acetate. The ethyl acetate layer was washed successively with water, aqueous sodium bicarbonate, and finally with water, and dried. Removal of the solvent gave a dark orange liquid. Semicarbazone was obtained by the usual method as a gray solid (0.1∼0.2 g.), which, when recrystallized from methanol or alcohol, underwent decomposition. Recrystallization from benzene—although the solubility in it was small—gave grayish white plates, m. p. 176~176.5°C (partly decomp.); yield, 30 mg.

Found: C, 42.08; H, 7.00; N, 36.79. Calcd. for $C_{12}H_{21}O_3N_9$: C, 42.47; H, 6.24; N 37.15%.

The aforesaid washings with aqueous sodium bicarbonate were acidified with sulfuric acid, yielding a grayish white solid. Recrystallization from water gave IX, m. p. 155~156° (partly decomp.). The black polymer, obtained in this reaction, was rather soluble in water, very soluble in alcohol or acetone, but insoluble in ether and ethyl acetate. Further investigation was given up, since the attempts of purification failed.

Since one of us (Kawai) must now give up his laboratory life, in consequence of his personal circumstance, we hope that anyone who feels interested in this field will persue the synthetical attack on the "dodecahedrane", the existence of which is theoretically possible.

We are indebted to the Ajinomoto Co. for the gifts of valuable compounds for the present research. Thanks are also due to the Science Research Institute and the Takamine Kenkyusho in the Sankyo Co. for microanlyses.

Department of Chemistry
Faculty of Science
Tokyo University of Education
Koishikawa, Tokyo